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Letter to the Editor

Re: Muñoz *et al.*, "Against which human papillomavirus types shall we vaccinate and screen? The international perspective." Int J Cancer 2004;111:278-85

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ABSTRACT

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LETTER

Re: Muñoz *et al.*, "Against Which Human Papillomavirus Types Shall We Vaccinate and Screen? The International Perspective." Int J Cancer 2004;111:278-85

Dear Sir,

The excellent article by Muñoz *et al.*[1] described the worldwide type distribution of human papillomaviruses (HPVs) and clarified which types are most important for vaccination and screening. This group has indisputably the best data regarding the distribution of individual HPV types in invasive cancers, the basis for projecting the clinical sensitivity of prevention efforts. Therefore, the 7 HPV types that they found most commonly in cervical cancers (HPV 16, 18, 45, 31, 33, 52 and 58) likely represent the types truly causing the largest burden of cancer in the world.

In their discussion, our colleagues addressed the issue of adding HPV types to vaccines and screening tests. We wholeheartedly agree that adding HPV types to an HPV vaccine does not present a major problem, if vaccinating concurrently against multiple HPV types proves not to cause any immunologic interference or increased side effects.[2] The numbers of HPV types feasibly incorporated into vaccines will depend on cost and the practical obstacles associated with carrying out polyvalent vaccine trials.[3]

With regard to screening tests, we would like to clarify a point that may have been misinterpreted by readers. Muñoz *et al.*[1] concluded that modifying the HPV tests currently used worldwide would have a relatively small impact on screening tests. While it is true that adding more HPV types to screening tests might do little to improve clinical sensitivity, we argue that it would have a serious, probably negative effect on clinical specificity.

HPVs are a nearly ubiquitous group of viruses that collectively achieve a lifetime cumulative incidence of up to 70%,[4] whereas cervical cancer is a relatively rare disease, with a lifetime incidence range of 1.1-3.0% across the world.[5] Simply put, the majority of women with HPV infection(s) will never develop cervical cancer or its precursors. Since the HPV DNA tests currently used or in development for screening use are pooled probe sets that generally test for HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68, the results are positive/negative rather than type-specific; therefore, inadvertent classification of HPV types as oncogenic has the potential to mislead many women into believing that they are at high risk for cancer.[6] Our colleagues' conclusion that modifications of the current HPV DNA testing system "are largely irrelevant if compared with the impact of achieving widespread screening coverage of the population or ensuring proper follow-up of HPV-positive women," while recognizing the need for expanded screening coverage and follow-up, does not acknowledge the specificity problems already inherent in HPV testing.

In a study to quantify the impact of adding HPV types to screening tests, we evaluated the sensitivity and specificity tradeoffs of testing for approximately 40 HPV types in a population of 10,000 Costa Rican women.[7] We iteratively generated all possible combinations of HPV types to simulate various pooled probe sets and found that, as we continued to add HPV types to our combinations, the tradeoff between specificity and sensitivity worsened substantially.[8] At the extreme, screening for a common HPV type that rarely causes cancer, such as HPV 53, would generate approximately 100 false-positives for every true detection of cervical intraepithelial neoplasia 3 or worse. When screening tests are applied to millions of women, a high ratio of false-positives to true-positives is troubling. False-positives in screening lead to unnecessary colposcopies, biopsies and ablational/excisional treatments, which increases both health-care costs and morbidity.[9]

In summary, Muñoz *et al.*[1] have shown that the prevalence of specific HPV types in invasive cervical cancers varies only slightly by worldwide region. We do not know whether the type variation is sufficient to motivate region-specific HPV vaccines and screening tests; however, cautionary planning to ensure a minimal false-positive rate should be the same regardless of area. A series of regional cost-utility studies performed separately for screening and vaccination would be the best basis for decision making.

Yours sincerely,

Michelle J. Khan, Rolando Herrero, Mark Schiffman

REFERENCES

1 Muñoz N, Bosch FX, Castellsague X, Diaz M, de Sanjose S, Hammouda D, Shah KV, Meijer CJLM. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. *Int J Cancer* 2004; **111**: 278-85. Links

2 Liaw KL, Hildesheim A, Burk RD, Gravitt P, Wacholder S, Manos MM, Scott DR, Sherman ME, Kurman RJ, Glass AG, Anderson SM, Schiffman M. A prospective study of human papillomavirus (HPV) type 16 DNA detection by polymerase chain reaction and its association with acquisition and persistence of other HPV types. *J Infect Dis* 2001; **183**: 8-15. Links

3 Lowy DR, Frazer IH. Prophylactic human papillomavirus vaccines. *J Natl Cancer Inst Monogr* 2003; **31**: 111-16. Links

4 Koutsky L. Epidemiology of genital human papillomavirus infection. *Am J Med* 1997; **102**: 3-8. Links

5 Parkin DM, Pisani P, Ferlay J. Global cancer statistics. *CA Cancer J Clin* 1999; **49**: 33-64. Links

6 Wright TC Jr, Schiffman M. Adding a test for human papillomavirus DNA to cervical-cancer screening. *N Engl J Med* 2003; **348**: 489-90. Links

7 Herrero R, Hildesheim A, Bratti C, Sherman ME, Hutchinson M, Morales J, Balmaceda I, Greenberg MD, Alfaro M, Burk RD, Wacholder S, Plummer M, et al. Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. *J Natl Cancer Inst* 2000; **92**: 464-74. Links

8 Schiffman M, Khan MJ, Solomon D, Herrero R, Wacholder S, Hildescheim A, Rodriguez AC, Bratti MC, Wheeler CM, Burt RD for the PEG Group and the ALTS Group. A study of the impact of adding HPV types to cervical cancer screening and triage tests. *J Natl Cancer Inst* 2005; **97**: 147-50. Links

9 Sadler L, Saftlas A, Wang W, Exeter M, Whittaker J, McCowan L. Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. *JAMA* 2004; **291**: 2100-6. Links